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08/242,023 05/11/94 BROWN

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EXAMINER
TUSCAN, M

18N1/1015

ART UNIT PAPER NUMBER

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1813

13

DATE MAILED: 10/15/94

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined Responsive to communication filed on _____ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. Notice of References Cited by Examiner, PTO-892.
2. Notice of Draftsman's Patent Drawing Review, PTO-948.
3. Notice of Art Cited by Applicant, PTO-1449.
4. Notice of Informal Patent Application, PTO-152.
5. Information on How to Effect Drawing Changes, PTO-1474..
6. _____

Part II SUMMARY OF ACTION

1. Claims 1-48 are pending in the application.

Of the above, claims 2-11, 16-25, 29-36, 40-46 are withdrawn from consideration.

2. Claims _____ have been cancelled.

3. Claims _____ are allowed.

4. Claims 1, 12-15, 26-28, 37-39, 47-48 are rejected.

5. Claims _____ are objected to.

6. Claims _____ are subject to restriction or election requirement.

7. This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. Formal drawings are required in response to this Office action.

9. The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are acceptable; not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been approved by the examiner; disapproved by the examiner (see explanation).

11. The proposed drawing correction, filed _____, has been approved; disapproved (see explanation).

12. Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has been received not been received been filed in parent application, serial no. _____; filed on _____.

13. Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. Other

EXAMINER'S ACTION

15. This application is a continuation of application 07/838,715. Claims 1-48 are pending.

16. Applicant's election with traverse of Invention I, claims 1, 12-15, 26-28, 37-39 and 47-48 in Paper No. 8 is acknowledged. The traversal is on the ground(s) that all pending claims are drawn to essentially the same invention, i.e. recombinant, non-fused VP1 protein. This is not found persuasive because Inventions II and III are not directed to the protein of Invention I. As set forth in Paper No. 6, Inventions II and III are drawn to transformed host cells and a measuring or testing process, respectively. Accordingly these inventions are distinct from the protein of Invention I.

The requirement is still deemed proper and is therefore made FINAL.

17. This application contains claims 2-11, 16-25, 29-36 and 40-46, drawn to an invention non-elected with traverse in Paper No.

8. A complete response to the final rejection must include cancellation of non-elected claims or other appropriate action (37 C.F.R. § 1.144) M.P.E.P. § 821.01.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition

under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

18. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

19. Claims 12, 13, 26, 27, 37 and 38 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

The specification has failed to provide evidence of a patentable utility for the vaccines of claims 12-13, 26-27 and 37-38. The art recognized definition of a vaccine encompasses the ability of the immunogen to elicit protective immunity to a secondary challenge. The applicant has not provided substantive evidence that the claimed vaccines are immunogenic and elicit protective immunity in human subjects or an appropriate animal model. The recognition of the instant proteins by human sera from infected donors is not indicative of the ability to elicit a protective immune response by administration of the instant proteins.

It is well established that a patent may not be granted on a chemical compound unless a utility is shown, other than that for experimental purposes only. The burden is on the applicant to demonstrate that the claimed products posses the claimed

biological activity. See Brenner v Manson 383 U.S. 519, 148 USPQ 689 (1966).

Applicants argue:

- (1) that Kurtzman et al, *J. Clin. Invest.* 84:1114-1123 (1988) demonstrate that antibodies against the B19 capsid proteins provide protection against B19 infections;
- (2) that Brown et al teach that the B19 virus and the claimed VP1-VP2 particles share epitopes in common; and
- (3) that results of Brown et al indicate that the claimed particles can function as vaccine carriers, i.e. can present heterologous epitopes to the immune system in a manner that induces protective immunity.

These arguments have been considered but are found unconvincing for a number of reasons. First, applicants have failed to demonstrate that the specific antibodies induced by the native B19 virus that appear to clear viral infection are also induced by the claimed particles or proteins. Furthermore, it is noted that the vaccines of claims 12, 13, 15 and 26 contain only one of the capsid proteins (VP1 or VP2), i.e., these vaccines cannot present all of the potential native capsid epitopes. It is well known in the art that the ability to induce protective immunity with a subunit vaccine can be problematic. The specification or supporting documents do not indicate that the individual proteins, even when in a capsid-like structure, present the epitope(s) that induce antibodies responsible for

viral clearance during the natural infection cycle. Many immunogenic epitopes are conformational, i.e. slight changes in a proteins secondary or tertiary structure can drastically affect the epitopes three dimensional structure. Although Brown et al demonstrate that some epitopes are shared between the native virus and VP2 particles, the article fails to indicate that the **protective** epitopes are shared. In summation, applicants have not demonstrated that the claimed vaccines are capable of inducing protective immunity, nor have applicants demonstrated that the in vivo neutralizing antibodies elicited by the native virus are also elicited by the claimed compositions.

The rejection of claims 47 and 48 under U.S.C. § 101 as lacking patentable utility is withdrawn in view of applicants evidence that a clinically significant immune response can be induced to the heterologous antigen when presented in the context of VP2.

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make

and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification fails to teach the use of the claimed recombinant proteins and particles as a vaccine as in claims 12-13, 26-27 and 37-38. Specifically, the specification fails to provide information such as the method of administration, the appropriate amount to administer, an effective vaccination schedule that elicits long-term protective immunity, what adjuvants are to be utilized, etc. Accordingly, the specification fails to provide an enabling disclosure for one of ordinary skill in the art to effectively use the claimed vaccines.

Applicants argue that the specification provides an adequate and complete disclosure to enable one of ordinary skill in the art to practice the claimed invention and that conventional details do not need to be set forth in the specification. Applicants further argue that the Brown manuscript sets forth the dosages and method of administration.

This argument has been considered but is found unpersuasive. As set forth above, applicants have failed to provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. Absent this information, the specification fails to provide the pertinent details needed to use the claimed vaccine. This information is not conventional. It is well known in the art that the dosage, adjuvant and method of administration

of each vaccine is dependent on the individual antigenic agent used. As to the Brown et al manuscript, the rejection of claims 47 and 48 as failing to teach how to use the vaccine to induce immunity to the heterologous (non-B19) infectious agent has been withdrawn.

The specification fails to teach the production of vaccines containing an "antigenically active" portion of VP1 or VP2 as in claims 12, and 26. The specification fails to describe the construction of baculovirus vectors containing an antigenically active portion of VP1 or VP2. Furthermore, the specification fails to provide information as to what portions of VP1 and VP2 are antigenically active. Therefore, in light of the limited teachings of the specification, and the lack of data indicating what portions of VP1 and VP2 are epitopes that elicit neutralizing antibodies, it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed.

Applicants argue that the vaccine can be based on a specific epitope from either VP1 or VP2. However, the specification is not enabled for vaccine compositions. See rejection *supra*. Furthermore, the specification fails to teach how to identify which immunogenic epitope(s) are capable of inducing protective immunity. It is well recognized in the art that the ability of small peptides to elicit an immune response is unpredictable. Ellis reviews some of the problems encountered when attempting to

stimulate an immune response to a small peptide. Ellis states that "in practice, the approach has several shortcomings relative to the use of whole proteins. In general, the antibodies elicited by the intact protein cross-react more effectively with both the protein and the pathogen on which it resides than do peptides elicited by an individual peptide. Furthermore, such antibodies bind with higher affinity and are present at a higher titer than those elicited by the peptide. Thus the duration of the immune response stimulated by a synthetic peptide is inferior than that stimulated by the intact protein" (see p.573, fourth full paragraph).

The specification teaches only the expression and subsequent particle formation of VP2. The specification fails to teach the formation of particles consisting of VP1 and VP2 as in claim 28. It is not clear that particles were formed from the co-expression of VP1 and VP2 in insect cells infected with the recombinant viruses. Therefore, in light of the limited teachings of the specification, it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed. See Ex Parte Forman, 230 USPQ 546.

Applicants have not specifically responded to this issue.

The specification fails to teach the construction of recombinant baculovirus vectors containing epitopes of proteins of other pathogens incorporated into the coding sequence for VP2, the expression of such proteins, and the subsequent particle

formation as in claim 39. The specification provides no information as to where the fusions would be made within VP2, whether the fusion protein would still form particles, or whether the fused epitope from another pathogen would be effectively presented at the surface of the recombinant particle. Therefore, in light of the limited teachings of the specification it would require undue experimentation for one of ordinary skill in the art to practice the invention as now claimed.

Applicants have not specifically responded to these issues.

22. Claims 12-13, 26-28, 37-39, and 47-48 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

23. Claims 12, and 26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12 and 26 are vague and indefinite in the recitation of "antigenically active portion". The meaning of antigenically active is unclear. Furthermore, it is not clear what fragment or portion of the protein applicant is referring to.

24. Claims 13, 27, and 48 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. The recitation of a specific use for a product does not further limit the previous claim.

Applicants have indicated a willingness to rewrite the claims. However, **willingness** to rewrite the claims does not overcome this rejection.

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claims 1 and 14 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ozawa et al (J. Virol. 61(8):2627-2630).

Ozawa et al disclose the B19 parvovirus capsid proteins generated in bone marrow mononuclear cells. Figure 1 shows the detection of the immunoprecipitated non-fused capsid proteins VP2 and VP1 that have molecular weights of 58 and 84 Kd, respectively. As it is not clear that there is any functional difference between the instant proteins and the proteins produced by Ozawa et al, and it is not clear if the instant proteins are in an isolated and purified form, the applicants claims are fully met by this reference.

Applicants have not specifically argued the merits of this rejection.

27. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

28. Claims 1, 12, and 13 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Sisk et al, and Cotmore et al in view of Smith et al, Pennock et al, Luckow et al and Wood et al.

If the applicant has support for the capsid protein VP1 being in isolated form, claims 1, 12, and 13 are unpatentable over the above references. Ozawa et al (J. Virol 61(8):2395-2406) disclose the transcription map of the B19 human parvovirus, including the location of the genes for the 84 Kd VP1 antigen and the 58 Kd VP2 antigen (p. 2403, Fig.9). Cotmore et al also

disclose the location of the VP1 and VP2 genes on the human parvovirus B19 genome by shotgun cloning restriction fragments from the cloned viral genome, expressing those fragments in E. coli, and detecting the expressed capsid polypeptides with diagnostic human anti-B19 serum. See Fig.4 for the location of the clone (pYT106) that expressed VP1 and VP2. Sisk et al disclose the expression of a VP1- β galactosidase fusion protein in E. coli that is recognized by anti-B19 serum. See Fig.4 and the first sentence of the discussion. Additionally, Sisk et al disclose the need to produce B19 viral capsid proteins by recombinant means as viral growth in tissue culture does not produce significant quantities of antigen (see Sisk et al, p. 1077, second paragraph). None of these references disclose the expression of VP1 or VP2 in recombinant baculovirus infected insect cells.

Wood et al disclose the expression of the VP-2 capsid protein from the related canine parvovirus from a recombinant baculovirus in insect cells. This protein was successfully utilized as a vaccine in dogs (see column 6).

Smith et al, Pennock et al, and Wood et al disclose the expression of heterologous proteins in infected insect cells using baculovirus as the vector. Smith et al recite on page 2164:

"...Baculoviruses should prove to be important vectors for the production of cloned gene products in insect cells or

organisms. The invertebrate cell will provide a unique biochemical environment for the production of foreign products and will complement vertebrate and prokaryotic host-vector systems. Potentially, any gene could be linked to the polyhedrin promoter, incorporated into the AcNPV genome, and efficiently expressed in infected cells."

Smith et al also disclose on page 2156 that in infected cells, AcNPV polyhedrin accumulates to high levels and constitutes 25% or more of the total protein mass in the cell, and is probably synthesized in greater abundance than any other protein in a virus infected eukaryotic cell.

See also page 404 of Pennock et al, where the attractive features of the AcNPV are described:

"(i) a capacity to accommodate large passenger DNA inserts in its expandable nucleocapsids, (ii) a strong promoter which allows for high level expression of fused passenger genes... Finally, baculoviruses have an additional level of biological safety which few other viruses have. They are known to infect only invertebrate, and the mechanism of organismal transfer primarily involves the occluded form of the virus."

Luckow et al further review the advantages of expressing heterologous proteins in the baculovirus-insect cell system. Luckow et al state that "recombinant proteins produced in insect

cells with baculovirus vectors are biologically active and for the most part appear to undergo post-translational processing to produce recombinant products very similar to that of authentic proteins". See under Biological Activity of Recombinant Proteins. Table 1 also discloses the successful expression of 35 foreign genes by baculovirus vectors, including many viral capsid or envelope antigens.

Given the art recognized need for the large scale production of the human parvovirus B19 capsid antigens as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as exemplified by Ozawa et al (J. Virol 61(8):2395-2406) and Cotmore et al, as well as the disclosed expression in E. coli of the B19 capsid protein, it would have been obvious to one of ordinary skill in the art to express the VP1 coding sequence in a recombinant host cell for the large scale production of capsid antigen. Furthermore, given the advantages of utilizing the commercially available baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, as well as the previously disclosed use of the baculovirus expression system to produce a vaccine consisting of the canine parvovirus VP2 antigen, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to clone the coding sequence for VP1 into a baculovirus expression vector to produce large quantities of capsid antigen and suggest its use as a vaccine composition. It is obvious to employ known

materials (genes and expression vectors) for their known and expected uses.

29. Claims 14, 26, and 27 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Cotmore et al, and Sisk et al in view of Smith et al, Pennock et al, Luckow et al and Wood et al.

If the applicant has support for the capsid protein VP2 being in isolated form, claims 14, 26, and 27 are unpatentable over the above references. As described above, Ozawa et al, Cotmore et al, and Sisk et al disclose the transcriptional patterns and thus the location of the VP2 coding sequence in the genome of human parvovirus B19 as well as the expression of the capsid protein in E. coli. Similarly, Smith et al, Pennock et al, and Luckow et al disclose the advantages of utilizing the baculovirus-insect cell expression system to produce large quantities of recombinant proteins. As described above, Wood et al disclose the production of a vaccine consisting of the canine parvovirus VP2 capsid protein using the baculovirus-insect cell expression system.

Given the art recognized need for the large scale production of the human parvovirus B19 capsid antigens as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as exemplified by Ozawa et al (J. Virol. 61(8):2395-2406), and Cotmore et al, as well as the disclosed expression in E. coli of the B19 capsid protein, it would have been obvious to one of

ordinary skill in the art to express the VP2 coding sequence in a recombinant host cell for the large scale production of capsid antigen. Furthermore, given the advantages of utilizing the commercially available baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, as well as the previously disclosed use of the baculovirus expression system to produce a vaccine consisting of the canine parvovirus VP2 capsid protein as exemplified by Wood et al, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to clone the coding sequence for VP2 into a baculovirus expression vector to produce large quantities of capsid antigen and suggest its use as a vaccine composition. It is obvious to employ known materials (genes and expression vectors) for their known and expected uses.

30. Claims 15, 28, 37, and 38 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Cotmore et al, Sisk et al, Smith et al, Pennock et al, Luckow et al, and Wood et al as applied to claim 14 above, and further in view of Kajigaya et al, Pintel et al, and Mazzara et al.

As described above the utilization of the baculovirus-insect cell expression system to produce large quantities of the human parvovirus B19 VP1 and VP2 capsid antigens would have been obvious to one of ordinary skill in the art. Pintel et al disclose the production of empty virion particles of the related

parvovirus MVM in recombinant murine cells. The particles were produced from bovine papillomavirus (BPV)-based vectors, in which were cloned the genome of MVM containing the VP1 and VP2 coding sequences. Kajigaya et al disclose the production of empty capsids of the B19 parvovirus from an engineered cell line that contains the B19 VP1 and VP2 coding sequences. Mazzara et al disclose the production of empty canine parvovirus capsids in eukaryotic cells that express VP1 and VP2. Mazzara et al further suggest the extension of this technique to produce antigenic empty capsids made from the human parvovirus VP1 and VP2. See page 5.

Given the art recognized need to produce large quantities of the B19 capsid protein for diagnostic and potential vaccine use as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as described in Ozawa et al (J. Virol. 61(8):2395-2406) and Cotmore et al, the advantages of using the baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, and the previously disclosed production of a vaccine consisting of the canine parvovirus VP2 expressed in the baculovirus-insect cell expression system, it would have been obvious to express the genes for VP1 and VP2 in the baculovirus expression system. Furthermore, given the art recognized ability of parvovirus VP1 and VP2 to form empty virions in other expression systems as exemplified by Pintel et al, Kajigaya et al, and Mazzara et al, it would have been

obvious, absent unexpected results, to produce empty virions consisting of VP2 or VP1 and VP2 in the baculovirus expression system and suggest their use in a vaccine composition.

31. Claims 3^a and 47-48 are rejected under 35 U.S.C. § 103 as being unpatentable over Ozawa et al (J. Virol. 61(8):2395-2406), Cotmore et al, Sisk et al, Smith et al, Pennock et al, Luckow et al, Wood et al, Kajigaya et al, Pintel et al, and Mazzara et al as applied to claim 15-28, and 37-38 above, and further in view of Evans et al, Borisova et al, and Clarke et al.

As set forth above, it would have been obvious to one of ordinary skill in the art to produce the claimed particles containing VP2 or VP1 and VP2 in the baculovirus expression system. Evans et al disclose the expression of an epitope of HIV-1 gp41 as a chimeric molecule inserted into the gene for the poliovirus capsid protein VP1. Clarke et al disclose the production of a vaccine consisting of an epitope from the capsid protein VP1 of the foot and mouth disease virus inserted into the coding sequence of HBcAg in E. coli. Borisova et al also disclose the use of the hepatitis B core antigen particles to express foreign antigens on the particle surface (HIV-1 gp41, and gp51 of bovine leukemia virus). See Table 1, p.123.

Given the art recognized need to produce large quantities of the B19 capsid protein for diagnostic and potential vaccine use as exemplified by Sisk et al, the previously disclosed genes for VP1 and VP2 as described in Ozawa et al (J. Virol. 61(8):2395-

2406) and Cotmore et al, the advantages of using the baculovirus-insect cell expression system as set forth by Smith et al, Pennock et al, and Luckow et al, and the previously disclosed production of a vaccine consisting of the canine parvovirus VP2 expressed in the baculovirus-insect cell expression system, it would have been obvious to express the genes for VP1 and VP2 in the baculovirus expression system. Furthermore, given the art recognized ability of parvovirus VP1 and VP2 to form empty virions in other expression systems as exemplified by Pintel et al, Kajigaya et al, and Mazzara et al, it would have been obvious, absent unexpected results, to produce empty virions consisting of VP2 or VP1 and VP2 in the baculovirus expression system. Additionally, given the art recognized utilization of human viral core or capsid proteins to express foreign antigens or epitopes of other pathogens, as exemplified by Evans et al, Clarke et al, and Borisova et al, it would have been obvious to one of ordinary skill in the art, absent unexpected results, to insert the antigenic epitopes of other pathogens into the parvovirus VP2 coding sequence, express the chimeric gene in the baculovirus-insect cell expression system, and produce empty capsid particles expressing the foreign antigenic epitope on the particle surface.

Applicants have not specifically argued the merits of each of the above rejections. Applicants do claim that the Kajigaya et al and Borisova et al references were published after the

priority date of the instant application. It is noted that both references were published prior to the PCT filing date (September 11, 1990) but after the filing of the Dutch application. However, applicants have failed to provide a translation of the 8902301 Dutch application. Absent this translation, it is impossible to determine if the application is enabling and provides an adequate written description of the instant claims. Accordingly, at this time, the Kajigaya et al and Borisova et al references qualify as prior art against the instant claims.

Applicants further argue:

- (1) the claimed invention is not obvious from the teachings and disclosures of the above references viewed separately or in any combination;
- (2) that the Examiner used applicants's own teachings in the specification to combine the references;
- (3) that it was unexpected that capsids could be formed expressing VP2 in the absence of VP1;
- (4) that it was unexpected that VP2 could be used as a diagnostic marker; and
- (5) that it was unexpected that VP2 capsids could be used as a carrier for heterologous epitopes.

These arguments have been carefully considered but are found unpersuasive for a number of reasons:

- (1) and (2) Hindsight was not used to combine the teachings of the above references. Furthermore, applicant's vague and

general argument that hindsight was used is insufficient to overcome the above rejections. Contrary to applicant's assertion, the prior art provided motivation to express VP1 and VP2 in the baculovirus expression system. Wood et al demonstrate and provide the methods of expressing parvovirus proteins in the baculovirus/insect cell expression system, both proteins had been previously cloned, and Smith et al, Pennock et al, and Luckow et al teach many of the art recognized advantages of expressing eukaryotic proteins in the baculovirus/insect cell expression system. Accordingly, applicants possessed both the methods, starting materials (cloned DNA) and motivation to produce the claimed proteins and particles. Obviousness does not require absolute predictability, but only a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673.

(3) Although, the native B19 capsid is composed of VP1 and VP2, it was well known in the art that the sequence of VP2 is completely contained within VP1 and that VP1 is present in the native capsid in minor amounts compared to VP2 . Accordingly, one of ordinary skill in the art would have expected that VP2 would contain the structural or functional elements or domains necessary for capsid formation. Furthermore, as it appears that particle formation is an inherent property of VP2 expression in eukaryotic cells, the recitation of "particle" is considered a further characterization of the protein, not a patentably distinct product.

(4) Applicant's assertion that it was unexpected that VP2 could be used as a diagnostic marker are not relevant to the instant claims. The instant claims are drawn to proteins, particles and vaccines, not diagnostic reagents, kits or methods.

(5) Applicant's assertion that it was unexpected that VP2 could be used as a carrier for heterologous epitopes is insufficient to overcome the rejections. Applicants have not provided reasons or justification for such an assertion. Furthermore, it was well known at the time of the invention that viral capsid proteins could be modified to present heterologous epitopes as exemplified by Evans et al, Clark et al, and Borisova et al. Applicant's arguments as the effects of the T cell epitopes of the HBV core antigen on heterologous T cell epitopes are not relevant to the instant claims. First, the limitation of a heterologous T cell epitope is not a limitation of the instant relevant claims. Furthermore, there is no indication that the T cell epitopes of any viral core antigen interfere with the immunogenicity of a known B cell epitope that would be used to induce protective immunity against human parvovirus infection. Contrary to applicant's assertion, the skilled artisan would expect that the core or capsid T cell epitopes would improve immunogenicity as a humoral immune response is augmented by the action of T helper cells.

33. This is a continuation of applicant's earlier application S.N. 07/838,715. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds or art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See M.P.E.P. § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

34. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center Telephone Numbers are (703) 308-4227 and (703) 305-3014.

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35. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Tuscan whose telephone number is (703) 308-4240. The Examiner can be reached Monday through Friday 7:30am to 5:00pm, E.S.T..

In instances when the Examiner can not be reached, Supervisory Patent Examiner Christine Nucker can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



CHRISTINE M. NUCKER
SUPERVISORY PATENT EXAMINER
GROUP 180


Michael S. Tuscan, Ph.D.
October 13, 1994